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Original Research Article

Profile of patients undergoing third line anti-retroviral therapy

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ABSTRACT

Background: India has the third largest human HIV epidemic in the world. The advent of antiretroviral drug began a revolution in the management of HIV. Recent studies have shown that an increasing number of patients experiencing virologic failure on second line Antiretroviral therapy and require third line ART.
Methods: This prospective cohort study was conducted in Regional Institute of Medical Sciences, Imphal for a period of two years, to study the clinical, immunological, and virological profile of patients undergoing third line Antiretroviral therapy and to study the early immuno-virological response to third line Antiretroviral therapy.
Results: Mean CD4 count before third line ART initiation was 95.90±111.85 cells/µl with 60% of them had CD4 count <100 cells/µl. The mean CD4 count improved significantly ($p<0.005$) to 246.70±123.78 cells/µl after six months and 340.70±198.57 cells/µl after one year of the therapy. At the time of initiation of third line ART, none of the patients had viral load <150copies/ml while 60% of the population had viral load >100000 copies/ml. After one year of third line ART, 80 % of the patients showed viral suppression (VL<150copies/ml). At the end of one year, the improvement in CD4 count comparing to the Viral load was significant in those who showed viral suppression (VL<150 copies/ml).
Conclusions: This study showed significant improvement in the CD4 count and viral suppression with third line medication without any major clinical adverse effect.

Keywords: ART, Darunavir, Failure, HIV, Raltegravir, Ritonavir, Third-line

INTRODUCTION

The national adult HIV prevalence in India is estimated at 0.22% in 2017 (0.25% among males and at 0.19% among Females).[1] Among the States, Mizoram has shown the highest estimated adult HIV prevalence of 2.04%, followed by Manipur 1.43%. The advent of antiretroviral drug in the early 1990s began a revolution in the management of HIV. There has been a rapid decline in the HIV related mortality and morbidity due to the wider availability of affordable, more efficacious and less toxic Antiretroviral (ARV) drugs over the last two decades. Successes achieved by Antiretroviral Therapy (ART) have now transformed the perception about HIV infection from being a 'virtual death sentence' to a 'chronic manageable illness'.[2] The primary goals of ART are maximal and sustained reduction of plasma viral levels and restoration of immunological functions.

As the HIV is prone to error during replications, some patients on second-line ART may also develop resistance to their regimen. This is particularly if the adherence of the patients was not good or they underwent late switching to second-line drugs.[3-5] These patients will

eventually require third-line ARV drugs. Recent studies have shown that an increasing number of patients experiencing virologic failure on second line Antiretroviral therapy and require third line ART. At least 6% of patients need third line ART after starting HAART.[6] Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens such as Integrase strand transfer inhibitors (INSTIs) and second-generation NNRTIs and PIs. Under the national programme, it has been decided to provide INSTI (Raltegravir) and a new boosted PI (Darunavir/ritonavir). Accordingly, the regimen is Raltegravir (400 mg) + Darunavir (600 mg) + Ritonavir (100 mg); one tablets each twice daily. As per WHO recommendations, in some cases the existing NRTI backbone can also be continued for the possible retention of some anti-retroviral activity.[7]

There are limited numbers of studies available about the patients profile in terms of effectiveness, response and adverse profiles of patients on third line ART. Further, Manipur being a high prevalent state, the findings about the profiles of these groups of patients would be significant in capturing the way third line ART impacts the outcome.

Aims and objectives of current research were to study the clinical, immunological, and virological profile of patients undergoing third line Antiretroviral Therapy and to study the early immuno-virological response to third line antiretroviral therapy.

METHODS

Study design: Prospective cohort study

Study setting**:** Department of Medicine, Centre of Excellence (CoE) ART Centre (jurisdiction includes Manipur, Mizoram, Nagaland, Meghalaya, Tripura, Arunachal Pradesh), in collaboration with Department of Microbiology, Regional Institute of Medical Sciences (RIMS), Imphal, India.

Study duration**:** This study was carried out for a period of 2 (two) years from September 2017 to August 2019.

Study population**:** HIV positive patients, initiated or undergoing third line antiretroviral therapy at the CoE ART Centre, RIMS Imphal.

Inclusion criteria**:** HIV patients, more than 15 years of age, undergoing or initiated with third line ART and consented were included.

Exclusion criteria**:** Those refused to participate in the study were excluded.

Sample size**:** All patients accessing third line Antiretroviral Therapy as per the SACEP, CoE RIMS recommendations during the period of the study. Five patients were already on third line medication before starting the study. During the study period, 23 patients with suspected second line failure attended CoE ART centre, RIMS, out of which, a total of 5 patients were eligible who were subsequently commenced with third line therapy. Henceforth a total of ten patients were studied and evaluated.

Sampling**:** Consecutive cases of HIV infected patients attending CoE ART Centre, RIMS Imphal satisfying the inclusion criteria and giving due consent and/or assent were enrolled.

Study variables:

Independent variables were age, sex, domicile, religion; mode of transmission; co-morbidities; duration of first line and second line ART.

Dependent variables were CD4 count; viral load; clinical parameters like complete hemogram, liver function test, kidney function test, lipid profile.

Study tools

Study tools were pretested questionnaires, confirmation of HIV- using ELISA/ rapid kit, sysmex five part cell counter, RANDOX Rx IMOLA auto analyser, CD4 count- automated analyser, fluorescence activated cell sorter (FACS), viral load study - Abbott RealTime HIV-1 machine with limit of detection (LOD) 150 copies/ml with 0.2 ml sample volume.

Definition of second line failure- as per NACO

If PVL >1000 copies/ml or CD4 count (cells/µl) is, below pre-second line treatment value or below 50% of peak on second line treatment value, or below 100 for two consecutive tests at least 10 months apart.

Definition of early response

Early response was defined as patients' clinico-immuno-virological response to third line antiretroviral therapy after one to one and half years follow up.

Procedure

Ethical approval for this study was obtained from Research Ethics Board, Regional Institute of Medical Sciences, Imphal. Permission was taken from project director CoE, RIMS. Informed written consent was taken from the patient/ patient party. All the selected patients were subjected to comprehensive questionnaire/ history taking/ thorough detailed examination. All the routine examination was done as per NACO recommendation. Blood sample was sent for CD4 count, viral load testing, routine investigations. Followed enrollment, the patients were followed for clinical assessment monthly, 6 monthly for the immunological (CD4 count) and viral load study.

Participants were followed for one to one and half year after enrollment of the study. Laboratory parameters were graded according to Division of AIDS (DAIDS)[8] grading criteria. All the data collected were documented and analysed statistically to draw a useful conclusion. Confidentiality was maintained by coding of patient's data and safe storage throughout the study. Descriptive and inferential statistical analysis was carried out in the present study.

RESULTS

The study was carried out in the Department of Medicine and CoE ART centre in collaboration with the Department of Microbiology, Regional Institute of Medical Sciences for a period of two years. During the study period, the patients attending SACEP for suspected second line failure were examined, out of which ten patients who were eligible for third line ART were included in the study. Out of the ten third line ART patients, 4 (40%) were in the age group of 41 to 50 years. Mean age of the study participants was 45.90±11.57 years. Out of them 7 (70%) were male and 3 (30%) were female. Out of the study subjects, majority were from Manipur (n=7; 70%) followed by Nagaland (20%) and Mizoram (10%) and most of them were followers of Christianity (n=7; 70%), while the remaining were Hindus (30%). Sexual route (90%) was the most common mode of transmission in these patients.

During enrollment, the baseline CD4 count of patients was recorded. 50% of the patients showed CD4 count <100 cells/µl at the time of diagnosis of HIV. The mean CD4 count at the time of HIV diagnosis was 121.80±82.53 cells/µl. The median duration of first line ART in study population was 58.7 months. All 10 patients were started on second line ART after the failure of first line ART. The median duration of second line therapy in study population was 38.1 months with majority (60%) of them had taken it for 12 to 36 months.

Before initiating third line ART, CD4 count of the study population was repeated. The baseline mean CD4 count of 121.80±82.53 cells/µl came down to 95.90±111.85 cells/µl after the failure of second line ART.

CD4 count of study population during the study period showed significant improvement after six months and after one year of follow up. The mean CD4 count of 95.90±111.85 cells/µl at the time of third line ART initiation improved to 246.70±123.78 cells/µl after six months and 340.70±198.57 cells/µl after one year of the therapy (Figure 2).The improvement in CD4 count was statistically significant after one year of third line ART (p value <0.05). At the end of one year the improvement in CD4 count comparing to the viral load was significant in those who showed viral suppression (VL<150 copies/ml) (Table 1 and 2). The CD4 count in relation with the viral load was showing upward trend in the graph in those whose viral load was less than 150 copies/ml at the end of one year (Figure 4). But those patients with viral load more than 150 copies/ml at the end of the study period didn't show much improvement.

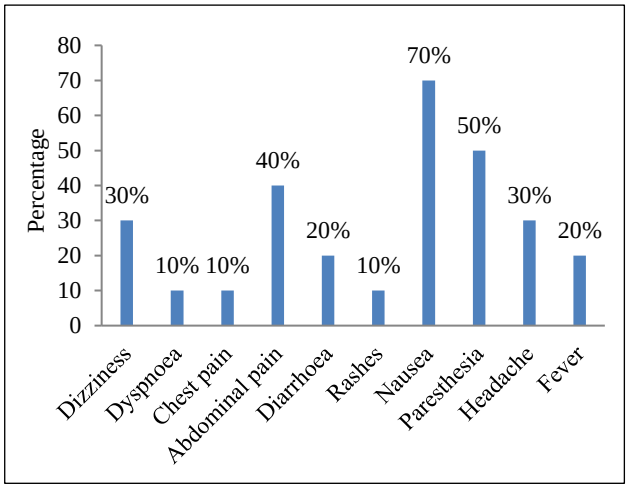

Figure 1: Drug related clinical adverse events during third line art (n=10).

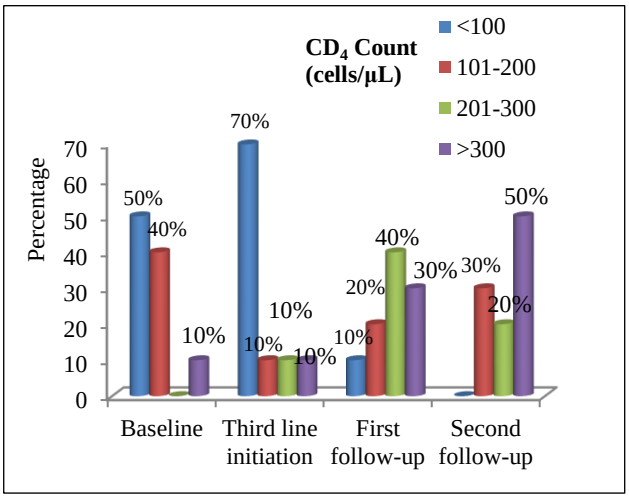

Figure 2: CD4 count at various stages (n=10).

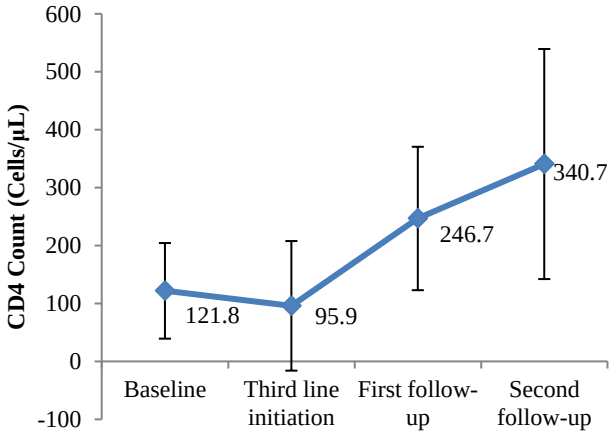

Figure 3: Pattern of mean cd4 count during follow up (n=10).

Table 1: Trend of viral load during the study period.

Viral Load (copies/ml)	Baseline N (%)	Third line initiation, N (%)	First follow-up N (%)	Second follow-up N (%)	Percentage difference
<150	0 (0)	0 (0)	0 (0)	8 (80)	0.0
150-10000	0 (0)	1 (10)	9 (90)	1 (10)	0.0
10001-1 lakh	1 (10)	3 (30)	0 (0)	0 (0)	-10.0
>1 lakh	9 (90)	6 (60)	1 (10)	1 (10)	-90.0

Table 2: Characteristics of Viral load in this study.

Viral load	Min-max (copies/ml)	Mean±SD (copies/ml)	Difference	P value
Baseline	24100.00-1600085.00	530276.70±561647.29	-	-
Third line initiation	4800.00-2248447.00	779429.10±916730.01	25.900	0.637
First follow-up	164.00-388000.00	41017.10±121948.54	-124.900	0.054
Second follow-up	150.00-31300.00	31329.00±98969.14	-218.900	0.020

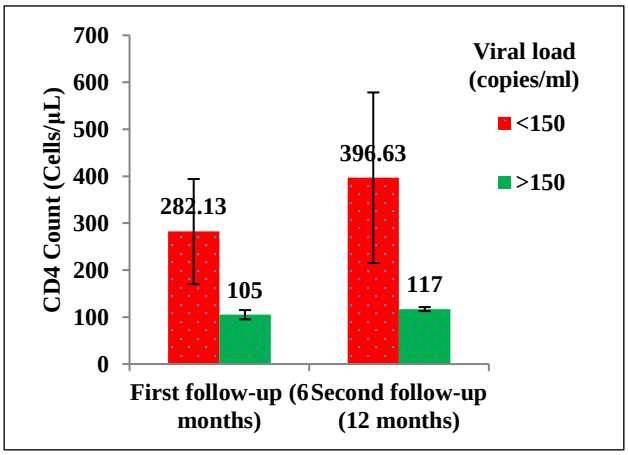

Figure 4: Relationship between CD4 counts and viral load in patient with viral failure and supressed viral load (n=10).

DISCUSSION

Antiretroviral drugs reduced the mortality and morbidity related to HIV. According to a study conducted by Cesar C et al, 6% of patients required third line antiretroviral therapy after 5 years of second line ART.[9] The main focus of the present study was to know the profile of the patients taking third line antiretroviral therapy and the early immuno-virological response to the treatment. A total of 10 patients taking third line antiretroviral therapy in CoE RIMS were included in the study with the mean age of 45.90±11.57 years. There were 70% of the study population were males and 30% were females. There were 18 patients taking third line ART in Mumbai were studied by Khan et al from 2011 to 2014.[10] In that study, the median age of the patients was 40 years and 75% of them were males.

Drug related adverse effects were common in patients taking antiretroviral treatment. In this study also, patients were affected by drug related clinical adverse effects, where nausea was the commonest symptom (70% of the patients) experienced by the patients followed by paraesthesia (50%), abdominal pain (40%), dizziness (30%), headache (30%) and fever (Figure 1). Study published by Eron et al on 2013 concluded that, the most common drug related side effects in patients taking raltegravir based salvage therapy, were diarrhoea, nausea and headache.[11]

Third line ART related studies were showing improvement in CD4 count after the ART initiation and also showing positive correlation between CD4 count and duration of the treatment (Figure 3, 4). In our study patients were followed for one year after initiating third line treatment for HIV. CD4 count at the time of diagnosis of HIV (baseline), before initiating third line treatment and 6 monthly after starting the medications were assessed. Mean CD4 count significantly improved from 95.90cells/µl at the time of third line initiation to 340.70cells/µl at the end of one year (mean CD4 count increased +245 cells/µl at the end of the study after one year with p value <0.001). Most of the studies related to third line HIV therapy showed significant improvement in CD4 count after one year of medication. A study by Pujari et al showed median CD4 gain at 12 months and 18 months were +283/mm^3, +393mm^3 respectively.[12] There were 80% of the study population (n=8) showed undetectable viral load after one year of third line medication. Two patients had viral load >1000 copies/ml at the end of our study period. Meintjes et al conducted a study, showed 74.5% patients had viral load <50 copies/ml after one year of therapy.[13] This study also showed the relationship between the CD4 count and the viral load. The mean CD4 counts at 6 months and one year were 282.13 cells/µl and 396.63 cells/µl respectively for the patients who showed viral load suppression comparing to the mean CD4 counts of 105.00 cells/µl and 117.00 cells/µl after 6 months and one year respectively in patients who showed virological failure. A study by Deshwal et al showed rapid detection in the viral suppression within 6 months which was not correlating with the increasing CD4 count.[14]

No mortality or morbidity was noted during the study period. None of the patients were left out during their follow up. The outcome of the study could help to improve the treatment options for patients failing second line ART and to know the effect and the side effect profile of the drugs. Due to financial constraints and logistic problem, resistance testing for the patients failing third line therapy could not be done by the researcher, and other limitation may be there due to inadequate sample size and short study period.

CONCLUSION

This study showed significant improvement in the CD4 count and viral suppression with third line medication without any major clinical adverse effect or death during the follow up. Findings of this study emphasises that third line ART is effective in patients who failed on second line ART without any major adverse events.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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